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10/519,311	12/22/2004	Roland Martin	4239-64111-05	9128

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KLARQUIST SPARKMAN, LLP
121 S.W. SALMON STREET
SUITE #1600
PORTLAND, OR 97204-2988

EXAMINER	
HISSONG, BRUCE D	
ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 08/11/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/519,311	MARTIN ET AL.	
	Examiner	Art Unit	
	Bruce D. Hissong, Ph.D.	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 March 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/22/04, 3/13/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Formal Matters

Claims 1-20 are currently pending and are the subject of this office action.

Information Disclosure Statement

1. The information disclosure statement received on 12/22/2004 has been fully considered by the Examiner.

2. The information disclosure statement received on 3/13/2006 has been fully considered by the Examiner.

Specification

The use of the trademarks Betaseron™, Avonex™, Rebif™, Zenepax™, and Simulect™ has been noted throughout the application. Trademarks should be capitalized wherever they appear and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks.

Claim Objections

1. The Examiner suggests the syntax of claim 14 can be improved by amending the claim to read ".....wherein the interferon-beta comprises interferon-beta 1a, interferon-beta-1, or combinations....."

2. The Examiner suggests the syntax of claim 20 can be improved by amending the claim to read "A method of treating multiple sclerosis comprising:.....", rather than "A method of treating multiple sclerosis comprising;....."

Claim Rejections - 35 USC § 112, first paragraph - enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The factors to be considered when determining if the disclosure satisfies the enablement requirement have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breath of claims. Ex Parte Forman, (230 USPQ 546 (Bd. Pat. App. & Int. 1986); In re Wands, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988).

Claims 1-6, as well as dependent claims 7-19, are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating multiple sclerosis by administration of interferon (IFN)-β and an interleukin (IL)-2 receptor antagonist that is an anti-Tac (including anti-Tac antibodies designated as Zenapax/daclizumab, basiliximab/Simulect, BT563, and 7G8), does not reasonably provide enablement for a method for treating any other autoimmune disease, or methods of treating multiple sclerosis using any other IL-2R antagonist. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The breadth of the claims is excessive because as written, the claims read on a method of treating any autoimmune disease by administration of IFN-β and an IL-2R antagonist. The specification of the instant application provides guidance and examples showing treatment of multiple sclerosis by administration of IFN-β and an IL-2R antagonist, but does not provide guidance or examples showing that any other autoimmune disease can be treated by the claimed method. It is well-known in the art that autoimmune diseases, which can include both

organ-specific and systemic diseases, have varied underlying causes and pathologies (see Goldsby *et al*, *Kuby, Immunology*, 4th Ed., 2000, p. 497-503), and therefore a person of ordinary skill in the art would not be able to predict which of the many possible autoimmune diseases could be treated by the claimed method. For example, would an antibody-mediated autoimmune disease such as autoimmune hemolytic anemia be treatable by the claimed method? Due to the unpredictability in the art with regards to the many underlying causes and manifestations of autoimmune diseases, a person of ordinary skill in the art would require further, undue experimentation to treat all possible autoimmune diseases by administration of IFN-β and an IL-2R antagonist.

The claims are also broad because they are drawn to the administration of any IL-2R receptor antagonist. Although the specification is enabling for the use of anti-Tac antibodies (Zenapax and daclizumab), there is no guidance or examples of any other type of IL-2R antagonist that can be used in the claimed method. Given the broadest possible interpretation, the claims can read on anti-Tac antibodies, but also on anti-IL-2R antibodies with different specificities, other polypeptide/peptide inhibitors, chemical inhibitors, or nucleic acids such as siRNA or antisense molecules specific for Tac/CD25. There is no guidance or examples in the specification showing that these, or any other potential IL-2R antagonist would be effective in treating an autoimmune disease when administered alone or in combination with IFN-β. Furthermore, due to the unpredictability regarding the biological effects of such a wide range of molecules, a person of ordinary skill in the art would not be able to predict which of the many possible IL-2R antagonists could be used to effectively treat multiple sclerosis, or any other autoimmune disease, without further, undue experimentation.

In summary, due to the excessive breadth of the claims, which read on methods of treating any autoimmune, the lack of guidance and examples in the specification showing that any autoimmune disease other than multiple sclerosis can be treated by the claimed method, and the unpredictability inherent in the art regarding which diseases other than multiple sclerosis can be treated, a person of ordinary skill in the art would require further, undue experimentation to practice a method for treating any autoimmune disease, other than multiple sclerosis, that is commensurate in scope with the claims as currently written. Furthermore, due to the excessive breadth of the claims, which also read administering any type of IL-2R antagonist, the lack of guidance and examples in the specification showing the efficacy of any IL-2R antagonist other than anti-Tac antibodies, and the unpredictability inherent in the art

regarding which of the many possible IL-2R antagonists could be used to treat any autoimmune disease, a person of ordinary skill in the art would require further, undue experimentation to determine which IL-2R antagonists, other than anti-Tac antibodies, could be used commensurate in scope with the claimed method of the instant application.

Claim Rejections - 35 USC § 112, first paragraph –written description

Claims 1-5, as well as dependent claims 6-19, are rejected under 35 U.S.C. 112, first paragraph, containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a method for treating an autoimmune disease comprising administering an IL-2R antagonist. The specification does not describe any IL-2R antagonist other than anti-Tac antibodies, and does not define any particular structural characteristics of an IL-2R antagonist. As discussed *supra*, the genus of IL-2R antagonists can consist of antibodies, fragments of antibodies, other polypeptide/peptide molecules, chemical inhibitors, and nucleic acids such as siRNA or antisense molecules. Thus, the claims are drawn to a genus of molecules that has not been adequately described in the specification.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claims is a requirement that the inhibitor antagonist the IL-2R. There is no identification of any particular portion of any IL-2R antagonist that must be conserved in order to maintain function. Accordingly, in the absence of sufficient distinguishing characteristics, the specification does not provide adequate written description of the claimed genus.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

1. Claims 1-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The pathology of autoimmune diseases can be manifested in a range of physical symptoms, and different types of autoimmune disease, including multiple sclerosis, can present with different symptoms (Goldsby *et al*; Paty *et al* – submitted in the information disclosure statement received on 12/22/2004). It is not clear what pathological feature or symptom(s) of any autoimmune disease, including multiple sclerosis, the claimed methods aim to treat. Thus, the metes and bounds of a "therapeutically effective combination" cannot be determined.

2. Claims 9, 11, 15, 17, and 18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims are indefinite because they recite the trademarks Betaseron, Avonex, Rebif, and Zenapax.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 20 is rejected under 35 U.S.C. 102(b) as being anticipated by "Study of Zenapax in the treatment of multiple sclerosis" (http://www.ms-network.com/pat/newsflash/show.asp?ID=143 - submitted with the information disclosure statement received on 12/22/2004). The claim is drawn to a method of treating multiple sclerosis in patients who were unresponsive to administration of IFN-β alone, wherein said methods comprises administration of a therapeutically effective dose of anti-Tac antibodies. The "Study of Zenapax" disclosure teaches a clinical study wherein Zenapax, which is taught by the instant specification to be an anti-Tac antibody (p. 3, 3rd – 4th paragraphs), is administered to patients that did not respond to IFN-β treatment. Because a clinical study of this type would

involve a method(s) of administering the anti-Tac antibodies to the subject, and the anti-Tac antibodies of the "Study of Zenapax" document would inherently have the same effect as the anti-Tac antibodies claimed in the instant invention, the disclosure of the "Study of Zenapax" document meets the limitations of claim 20 of the instant invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over the "Study of Zenapax" document, in view of Khoury *et al* (submitted with the information disclosure statement received on 12/22/2004), and further in view of Paty *et al* (submitted with the information disclosure statement received on 12/22/2004) and Jacobs *et al* (Ann. Neurol. 1996, Vol. 39, p. 285-294). The claims of the instant application are drawn to a method of treating an autoimmune disease, and specifically multiple sclerosis, wherein said method comprises administering IFN-β and an IL-2R antagonist. The claims are further drawn to administration of IFN-β-1a and IFN-β-1b, either alone or together, and in some embodiments, specifically recites administration of Avonex or Rebif (IFN-β-1a) or Betaseron (IFN-β-1b). The claims are also further drawn to administration of the anti-Tac antibody daclizumab or Zenapax.

As discussed *supra*, the "Study of Zenapax" disclosure describes a clinical trial wherein the IL-2R antagonist Zenepax, which is taught by the specification to be the trademark name for dacluzimab and an anti-Tac antibody, and thus an anti-IL-2R antagonist, is administered to patients with multiple sclerosis. Thus, the "Study of Zenapax" document discloses treatment of multiple sclerosis with an IL-2R antagonist (anti-Tac, dacluzimab, Zenapax). The "Study of Zenapax" document does not teach co-administration of any IFN-β.

Khoury *et al* does not teach a method of administration of IFN-β or an IL-2R antagonist to a subject with multiple sclerosis, but does teach that changes in activated T lymphocyte populations correlate with progression of multiple sclerosis. Specifically, Khoury *et al* found a strong correlation between the percentage of $CD25^+$ (i.e. Tac^+) T lymphocytes and the incidence

of multiple sclerosis attacks/relapses, as well as the resulting changes in patient disability (see abstract; p. 1187, 2nd column).

Paty *et al* and Jacobs *et al* teach administration of IFN-β-1b and IFN-β-1a, respectively, to patients suffering from multiple sclerosis. The disclosures of both documents indicate that both IFN-b molecules are effective in treating multiple sclerosis. Paty *et al* describes IFN-β-1b-treated patients with decreased brain inflammation, as evidenced by decreases in the number of lesions detected by MRI (abstract, p. 664-665), while Jacobs et al teaches that IFN-β-1a-treated patients had significantly fewer exacerbations and a decreased number and volume of brain lesions as determined by MRI (abstract).

It would have been obvious to one of ordinary skill in the art, at the time the instant invention was conceived, to combine the teachings of Paty *et al* and Jacobs *et al* with the disclosure of the "Study of Zenapax" document to practice a method of treating multiple sclerosis by administering IFN-β and an IL-2R antagonist. Although the "Study of Zenapax" document does not recite results of the study, Khoury *et al* teaches that the expression of CD25/IL-2R correlates with disease progression, and therefore, the numbers of activated T lymphocytes increases as the disease progresses or relapses. It has long been known in the art that IL-2 is a growth factor for activated lymphocytes, which express the CD25/IL-2R, and a person of ordinary skill in the art would know that interfering or inhibiting IL-2 signaling in T lymphocytes is advantageous in controlling T cell activation in pathological conditions involving excessive numbers of activated T cells. In the instant case, Khoury *et al* teaches that the progression of multiple sclerosis is characterized by increased numbers of CD25/IL-2R-expressing T lymphocytes, and therefore a person of ordinary skill in the art would expect the treatment disclosed in the "Study of Zenapex" document to be successful.

Additionally, by teaching that both IFN-β-1a and IFN-β-1b are effective in treating multiple sclerosis, the teachings of Jacobs *et al* and Paty *et al*, respectively, would provide the motivation to use these IFNs in a method of treating multiple sclerosis. By extension, the skilled artisan would also be motivated to practice methods of treating multiple sclerosis by using Betaseron as the IFN-β-1b, and Avonex or Rebif as the source of IFN-β-1a.

Furthermore, because the combined teachings of the "Study of Zenepax" disclosure, Khoury *et al*, Paty *et al*, and Jacobs *et al* teach that anti-Tac, IFN-β-1a, and IFN-β-1b are all individually effective in treating multiple sclerosis, the skilled artisan would be motivated to combine different treatments into one method of treatment. Therefore, the skilled artisan would

have both the motivation, and a reasonable expectation of success, in practicing a method of treating multiple sclerosis by administration of IFN-β-1a and/or IFN-β-1b, either alone or in combination with anti-Tac antibodies. In essence, if two or more individual treatments are effective in treating a disease, it is obvious to combine them into one method of treatment. Thus, claims 1-7 and 13-16 are obvious in view of the combined teachings of "Study of Zenapax", Khoury *et al*, Paty *et al*, and Jacobs *et al*.

Finally, although the combination of "Study of Zenapax", Khoury *et al*, Paty *et al*, and Jacobs *et al* does not explicitly teach the dosages, timing of administration, or route of administration of claims 8-12 and 17-19, one of ordinary skill in the art would have both the motivation, and the ability, to optimize these variables. Such optimization would be within the skilled artisan's abilities, an assertion that is supported by the instant specification (for example, see p. 9, 3rd full paragraph; p. 11, 3rd paragraph), and therefore claims 8-12 and 17-19 are also obvious in view of the combined teachings of "Study of Zenapax", Khoury *et al*, Paty *et al*, and Jacobs *et al*.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim 20 is provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-21 and 29-34 of copending Application No.

10/607,598. Although the conflicting claims are not identical, they are not patentably distinct from each other. Claim 20 of the instant application is drawn to a method of treating a subject with multiple sclerosis who was unresponsive to treatment with IFN-β alone, wherein said method comprises administering a therapeutically effective dose of anti-Tac. Claims 1-21 and 29-34 of the '598 application recite methods of treating a subject with multiple sclerosis who was unresponsive to IFN-β treatment, wherein said method comprises administering an IL-2R antagonist, which can be an antibody that binds the IL-2R, and includes the anti-Tac antibody daclizumab.

It would be obvious to a person of ordinary skill the art to practice the method of claim 20 of the instant application by using the methods set forth in the '598 application. Both applications recite treatment of multiple sclerosis patients who did not respond to treatment with IFN-β, and thus are seeking to treat the same patient population. Furthermore, both applications are drawn to methods of administering an IL-2R antagonist, and both applications recite the use of antibodies, such as anti-Tac/dacluzimab, that specifically bind the IL-2R. Although claim 20 of the instant application does not recite any specific doses or timing of administration, one of ordinary skill in the art would easily be able to optimize these variables and practice a method that is commensurate in scope with the methods set forth in the '598 application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

No claim is allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bruce D. Hissong, Ph.D., whose telephone number is (571) 272-3324. The examiner can normally be reached M-F from 8:30am - 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol, Ph.D., can be reached at (571) 272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

BDH
Art Unit 1646

ROBERT S. LANDSMAN, PH.D.
PRIMARY EXAMINER